



## Neuropathy and presence of emotional distress and depression in longstanding diabetes: Results from the Canadian study of longevity in type 1 diabetes



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### ABSTRACT

**Aim:** To determine the association of neuropathy and other complications with emotional distress and depression among patients with longstanding type 1 diabetes (T1DM).

**Methods:** Canadians with  $\geq 50$  years of T1DM completed a questionnaire including assessment of distress and depression by the Problem Areas in Diabetes Scale (PAID) and Geriatric Depression Scale (GDS), respectively. Complications were determined using the Michigan Neuropathy Screening Instrument (Questionnaire Component), funduscopy reports, renal function tests, and self-reported peripheral-(PVD) and cardiovascular (CVD) disease. Associations were analyzed by Poisson regression.

**Results:** Among 323 participants, 137 (42.4%) had neuropathy, 113 (36.5%) nephropathy, 207 (69.5%) retinopathy, 95 (29.4%) CVD, and 31 (9.8%) PVD. The neuropathy subgroup had higher prevalence of distress (13 (9.5%) vs. 6 (3.3%),  $p = 0.029$ ) and depression (34 (24.9%) vs. 12 (6.5%),  $p < 0.001$ ). Adjusting for diabetes complications, neuropathy was associated with higher PAID (adjusted RR 1.44 (95% CI 1.14–1.82),  $p = 0.003$ ) and GDS scores (adjusted RR 1.57 (1.18–2.11),  $p = 0.002$ ). Independent of potential confounders, neuropathy remained associated with higher PAID (adjusted RR 1.39 (1.10–1.76),  $p = 0.006$ ) and GDS scores (adjusted RR 1.37 (1.03–1.83),  $p = 0.032$ ). Associations with neuropathy were not fully explained by neuropathic pain.

**Conclusion:** Compared to other complications, neuropathy had the greatest association with distress and depression in longstanding T1DM, independent of pain. Strategies beyond pain management are needed to improve quality of life in diabetic neuropathy.

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### 1. Introduction

Type 1 diabetes mellitus (T1DM) places physical, psychosocial, and behavioral demands on patients and requires lifelong adherence to

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intensive therapy.<sup>1,2</sup> In older patients with longstanding T1DM, these demands may be augmented by the higher risk of complications including neuropathy, retinopathy, nephropathy, and cardiovascular disease (CVD).<sup>3</sup> Many studies have demonstrated an association between diabetes, diabetes complications and impairment in mental health,<sup>1–5</sup> and particular emphasis has been placed on the association between painful diabetic sensory neuropathy with depression.<sup>6</sup> However, the long-term association between diabetes-related emotional distress and depression with diabetes complications is not known: Specifically, it is unknown if both distress and depression are most strongly related to the presence of diabetic sensory neuropathy

compared to other complications and, in turn, if neuropathic pain is the key mediator. This is especially important to determine in elderly patients with T1DM due to their susceptibility to complications and poor mental health outcomes.<sup>3</sup>

Depression and distress are two major psychiatric outcomes in diabetes, and both are elevated in patients with diabetes of all age groups.<sup>1,7,8</sup> Depression refers to an affective disorder characterized by symptoms including sad or irritable mood, cognitive or somatic changes, and suicidal ideation.<sup>9</sup> To screen for major clinical depression in elderly patients, the Geriatric Depression Scale (GDS) was developed by Yesavage et al., and was later shortened to a 15-item questionnaire. Subsequently, the GDS-15 has been validated against several popular depression scales and in various populations, demonstrating sensitivity of 71%–100% and specificity of 78%–85%.<sup>10–14</sup> The questionnaire focuses on mood, life satisfaction, behaviors, and cognitions, but not on somatic manifestations of depression as these symptoms are confounded by those of complex medical illness and frailty. Furthermore, the yes/no format of GDS permits effective self-administration in older persons. These characteristics support the use of the GDS over other tools in older patients with longstanding diabetes and complications.

Diabetes-related distress – a negative emotional response to the burdens of diabetes and management – is a distinct concept from depression, as the former is specific to the psychological, physical, and social burdens of diabetes.<sup>1,15,16</sup> However, distress and depression share many common symptoms and have been shown to be highly correlated in T1DM.<sup>1,17,18</sup> The Problem Areas in Diabetes scale (PAID) is a validated 20-item questionnaire measuring distress in areas like anger, frustration with management, fear of complications, and social challenges related to diabetes care.<sup>19</sup>

Diabetic neuropathy has been shown to be independently linked to depression, distress and reduced quality of life – especially in older patients – though the mechanisms driving this interaction are not completely understood.<sup>1,20–22</sup> Previous studies have suggested that it is the painful symptomatology associated with sensory neuropathy that contributes to poor psychological outcomes.<sup>20,21</sup> However, some evidence shows that poor psychological outcomes in neuropathy stem from non-pain factors such as restricted quality of life, perception of symptom and treatment unpredictability, and changes in social self-perception.<sup>22,23</sup> Elucidating the link between neuropathy and its psychological sequelae may allow for more comprehensive management of diabetic neuropathy.

There is a paucity of evidence on neuropathy and psychological outcomes in older patients with longstanding T1DM, despite the key role of diabetes duration in predicting depression and distress.<sup>1</sup> In a unique cohort of older patients with 50 years or more of T1DM, we aimed to determine the magnitude of diabetes distress and depression, as well as the impact of symptomatic diabetic neuropathy and neuropathic pain on these psychological outcomes.

## 2. Research design and methods

### 2.1. Study overview and participants

This cross-sectional cohort study was conducted as a secondary analysis of data from the Canadian Study of Longevity in Type 1 Diabetes.<sup>24,25</sup> The goal of this analysis was to explore levels of emotional distress and depression in individuals with 50 years or more of T1DM, as well as to determine the independent effect of neuropathy on these psychological outcomes.

Between April 2013 and December 2014 patients with T1DM were contacted across Canada with support from the Canadian Diabetes Association and Juvenile Diabetes Research Foundation (JDRF) Canada, and through public advertisements, social media, and mailings to health care professionals including primary care physicians, endocrinologists, and pharmacists. Akin to other cohorts, our

study included patients with a history of at least 50 years of insulin dependence, as acknowledged through medical documentation or corroboration by a family member.<sup>26</sup> All participants provided written informed consent, and the study protocol was approved by the ethics committee of the Mount Sinai Hospital (Toronto, ON, Canada).

### 2.2. Data collection

Data were collected through a 35-page questionnaire in which participants were asked about their diabetes management, history of diabetes-related complications, cardiovascular (CVD) and peripheral vascular (PVD) disease, neuropathic symptoms, current medication use (including antidepressants and neuropathic pain medications), and psychological well-being. We used a combination of objective data, validated questionnaires, and self-reported outcomes to evaluate diabetes management, physical activity, and complications. With the participants' consent, we communicated with their healthcare providers to obtain recent clinical and laboratory measurements including blood pressure, HbA1c, kidney function, and fundoscopy examination results.

#### 2.2.1. Complications

Presence of symptomatic neuropathy was determined through the use of the 15-item, self-administered Michigan Neuropathy Screening Instrument (MNSI) questionnaire, for which symptomatic neuropathy was defined by a score  $\geq 3$  according to a detailed diagnostic analysis in patients with T1DM, a finding which refuted previous historical threshold values.<sup>27</sup> To study the severity and manifestations of sensory neuropathy, participants were asked, separate from the MNSI questionnaire, about the nature of symptoms including numbness in the extremities, tingling and pain, feet and leg involvement, loss of temperature sensation, sexual dysfunction, autonomic manifestations, ulcers, and amputations. Painful neuropathy was defined by MNSI  $\geq 3$  in addition to presence of any of self-reported tingling/pain/burning in the extremities, allodynia, or use of medications for neuropathic pain. Nephropathy was defined by a urine albumin to creatinine ratio (ACR)  $\geq 2$  mg/mmol if on a renin-angiotensin-system blocker (RASB) and  $\geq 3.4$  mg/mmol if otherwise, or an age-adjusted glomerular filtration rate (GFR)  $< 60$  ml/min as per the four-variable Modification of Diet in Renal Disease (MDRD) Study equation.<sup>28</sup> Fundoscopy results were used to establish the presence of retinopathy, defined by the presence of proliferative or non-proliferative morphological changes. Cardiovascular disease (CVD) was defined as self-reported history of angina, myocardial infarction, or cardiac bypass and angioplasty surgery. Peripheral vascular disease (PVD) was ascertained separately from CVD and was defined as a history of leg bypass surgery or angioplasty.

### 2.3. Assessment of emotional distress and depression

To assess diabetes-related emotional distress and depression, participants completed the 20-item PAID and 15-item GDS questionnaires. Each item in the PAID scale is scored on a Likert scale from 0 to 4, and the sum of scores is multiplied by 1.25 to give a maximum score of 100; a score  $\geq 40$  identifies the presence of clinically-relevant degree of emotional distress.<sup>29</sup> The GDS scale consists of 15 binary questions with a maximum score of 15. Scores of 0 to 4 are considered as no depression, 5 to 9 as mild depression, and 10 to 15 as severe depression.<sup>30</sup>

### 2.4. Statistical analysis

SAS version 9.2 (SAS Institute, Cary, NC, USA) was used to perform statistical analysis. Based on Canadian 1962 census data and contemporaneous age-specific incidence rates of type 1 diabetes and survival curves,<sup>32,33</sup> we hypothesized the existence of 1450

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